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Stroke Prevention, Evaluation of Bleeding Risk and Anticoagulant Treatment Management in Atrial Fibrillation Contemporary International Guidelines

Short Title: International AF Guidelines

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SUMMARY

In contemporary international guidelines on the management of atrial fibrillation, there is general agreement about the baseline evaluation of thromboembolic and bleeding risk and preferential use of NOACs. Notwithstanding the broad agreement, more data are needed about management of specific AF sub-populations. The need for an integrated approach and holistic management is highlighted in the more recently published guidelines.

ABSTRACT

In recent years the management of AF patients has progressively and substantially changed due to the introduction of new treatments and the availability of new data regarding the epidemiology and clinical management of these patients. In the last two years alone, there have been seven new guidelines or guideline updates that have been published, introducing new recommendations and significantly revising previously published ones. Two updates for Canadian guidelines were published in 2016 and 2018, while guidelines from the European Society of Cardiology in 2016, Asia Pacific Heart Rhythm Society in 2017, National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand, American College of Chest Physicians and Korean Heart Rhythm Society in 2018 have been published. This narrative review aims to provide a comparison of these contemporary international guidelines, with particular attention on the evaluation of thromboembolic and bleeding risks and management of OAC therapy.

From the analysis of contemporary guidelines on the management of atrial fibrillation, a general agreement is evident about the baseline evaluation of thromboembolic and bleeding risk, as well as a preference for the use of NOACs. Also, regarding the concomitant use of OAC and antiplatelet drugs in patients with acute coronary syndromes, undergoing elective percutaneous coronary intervention, catheter ablation and cardioversion procedures, all the guidelines agree on the general principles and are supported by evidence. More data are still needed to better substantiate recommendations for specific AF sub-populations. The need for an integrated approach and holistic management is highlighted in the more recently published guidelines.

Introduction

In the last ten years, clinical practice on stroke prevention in patients with atrial fibrillation (AF) has markedly changed[1]. The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) as an alternative to the vitamin K antagonists (VKAs)[2], has significantly increased the prescription and use of oral anticoagulant (OAC) therapy in AF patients, as demonstrated by several epidemiological and observational studies[3–6].

There has been much interest in expanding the understanding of AF pathophysiology, epidemiology and natural history, leading to an increasing number of papers on AF being published [Figure 1]. The deluge of data available has informed how several new issues are managed and have led to a change in clinical practice regarding patients with AF, both regarding the evaluation and reduction of thromboembolic risk as well as the general management of such patients. There is also an increasing focus on how the risk of cardiovascular and all-cause death is becoming an even more relevant issue in clinical history and clinical management of these patients[7–10]. This change in the risk profile has led to appeals for a new approach to the management of AF patients, involving a more integrated and holistic approach[11,12].

In the last two years alone, there have been several new guidelines or guideline updates that have been published, introducing new recommendations and significantly revising the previously published ones[13–19]. This narrative review aims to provide a comparison of these contemporary international guidelines or updates,

with particular attention to the evaluation of thromboembolic and bleeding risks and management of OAC therapy.

Overview and General Features of Contemporary International Guidelines

We provide an overview of the new guidelines published in the last two years[13–19]. General characteristics of these new guidelines are reported in Table 1.

In 2016 the Canadian Cardiovascular Society (CCS) published an update[13] to their 2010 AF clinical guidelines[20], while in 2016 the European Society of Cardiology (ESC) published their new guidelines[14], completely revising the previous main guideline from 2010 and the 2012 focused update[21,22]. In 2017, the Asia Pacific Heart Rhythm Society (APHRS) published their guidelines on stroke prevention in AF[15]. Finally, three entirely new guidelines in 2018 from National Heart Foundation of Australia (NHFA)/Cardiac Society of Australia and New Zealand (CSANZ)[16], from the American College of Chest Physicians (ACCP)[17] and Korean Heart Rhythm Society (KHRS)[19] with a second focused updated from the CCS guidelines[18] were published in 2018.

Five out of seven guidelines performed a systematic search of currently available evidence based on a structured and established technique used in evidence-based practice to frame and answer clinical or health related questions, the PICO (Population, Intervention Comparison, Outcomes) both in its original or modified form or the clinical questions model[13,14,16–18]. Conversely, the APHRS and KHRS guidelines were substantially based on expert consensus review[15,19]. The 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE)

methodology was used to evaluate the quality of scientific evidence in four of the seven guidelines[13,16–18]. Heterogeneity was evident in the grading of the strength of the recommendations and quality of evidence, with APHRS guidelines not explicitly grading their recommendations[15] and with KHRS ones only grading a limited number of recommendations[19]. Concerning conflict of interests, only the ESC, NHFA/CSANZ and ACCP guidelines[14,16,17] provided detailed disclosure of direct, indirect and potential conflict of interests, with the latter, ACCP, prohibiting voting on those issues for which an author reported a potential conflict of interest.

While we found a considerable variability regarding the classification of clinical types of AF, in particular related to the use of new onset/first detected AF and long-standing persistent AF, there was a substantial agreement across the various guidelines regarding the definition of non-valvular AF which is generally considered as the absence of mitral stenosis, even though some guidelines specifically stated the differential rheumatic or non-rheumatic origin and the degree of disease, and of mechanical heart valve. Notwithstanding, two guidelines did not assess the definition[15,19].

Evaluation of Thromboembolic Risk Evaluation and OAC Prescription

When evaluating thromboembolic risk (Table 2), most guidelines recommended the use of CHA_2DS_2-VASc score[14–17,19], although the NFHA/CSANZ guidelines used a modified CHA_2DS_2-VA score, that no longer consider the role of sex category in guiding the baseline OAC prescription[16]. This modification of the CHA_2DS_2-VASc score in the NFHA/CSANZ guidelines was justified by differential cut-offs for male and female AF patients or recommendations to exclude the sex category in the

evaluation by other guidelines(Table 2)[14,15,17,19]. The 5 guidelines using CHA_2DS_2-VASc score, recommend prescribing OAC therapy in all patients with at least 1 non-sex related risk factors[14–17,19]. Nonetheless, in the ESC, NHFA/CSANZ and KHRS guidelines, two differential recommendations are provided about patients with only 1 stroke risk factor and for 2 or more stroke risk factors[14,16,19]. While in the latter (CHA_2DS_2-VASc score ≥2) OAC is recommended, with a strong recommendation based on a high level of evidence, the level of evidence regarding the recommendation for patients with CHA_2DS_2-VASc score of 1 is lower, given that fewer such patients were included in the randomised trials.

In the 2018 ACCP guidelines, the overall recommendation of prescribing all patients with at least 1 stroke risk factor is a stroke recommendation based on moderate quality of evidence[17]. Of the most recent guidelines, ACCP and KHRS also underline how, on the basis of some recent evidence, stroke risk assessment needs to be considered a dynamic process and should be reassessed at the regular follow-up visits[17,19].

The Canadian guidelines differ from other guidelines since the evaluation of thromboembolic risk is based on the CHADS-65 algorithm, also known as the CCS algorithm[13,18]. This algorithm is a three-step evaluation scheme, that recommends evaluating the patient's age first, with all patients aged ≥65 years old recommended for OAC, followed by assessment of the presence of stroke risk factors according to the $CHADS_2$ risk score[23], where patients with at least 1 risk factor should receive OAC, and lastly evaluating the presence of coronary artery disease (CAD) or other arterial vascular disease, recommending the prescription of aspirin in those patients

aged <65 years with isolated CAD[13,18]. The Canadian guidelines remain the only one still recommending the use of aspirin in AF patients aged <65 years with isolated CAD and no other $CHADS_2$ stroke risk factors. Conversely, all other guidelines firmly recommend against the use of antiplatelet therapy for thromboembolic risk treatment[14–17,19].

When OAC is indicated, all guidelines agree about the preferential use of NOACs over VKA therapy[13–19], with most giving this a strong recommendation,[13,14,18,19] All guidelines concurred with the use of VKAs in patients with valvular AF. Where VKAs are used, most guidelines (ESC, APHRS, ACCP, KHRS) recommend to maintain a high quality of OAC control, expressed as time in therapeutic range (TTR) ≥65-70%[14,15,17,19].

Evaluation of Bleeding Risk

After the evaluation of thromboembolic risk, all guidelines point the attention to the bleeding risk evaluation (Table 3). Most strongly recommend the use of the HAS-BLED risk score to evaluate bleeding risk, with a moderate to a high quality of evidence[13,15,17–19]. The ESC guidelines underline how the use of clinical risk scores could be helpful tools in evaluating bleeding risk, but do not recommend one scheme over another[14]. Nonetheless, the ESC guidelines underline how, irrespectively of the score used, the main aim is to be to identify those patients with modifiable or potentially modifiable bleeding risk factors[14].

All guidelines agreed that a high bleeding risk should generally not be considered as a reason to withhold OAC treatment, except those specific situations when the

risk/benefit ratio excessively favours no antithrombotic[13–19]. Instead, efforts should be used to identify all the modifiable bleeding risk factors and address them where possible, discussing these with the patient, and providing more frequent and regular checks and follow-up visits[13–19]. Similarly to thromboembolic risk, ACCP and KHRS guidelines recommend a reassessment of bleeding risk on a regular basis in light of its dynamic impact on bleeding risk[17,19].

Utility of Left Atrial Appendage Closure

All the guidelines agreed that left atrial appendage (LAA) closure should not be routinely used for the management of thromboembolic risk in patients with AF (Table S1). While the Canadian guidelines suggest, with a low quality of evidence, that LAA closure should be considered only as part of the ablation procedure, even though clearly contraindicated in patients at high risk of stroke[13,18], other guidelines recommend that LAA closure should only be considered in those patients with absolute contra-indications to OAC use[14–17,19]. Overall, the guidelines judged the quality of evidence regarding LAA closure to be low.

Management of OAC and Antiplatelet Therapy

Several epidemiological studies have shown that AF is often associated with acute coronary syndrome (ACS) and myocardial infarction (MI)[24–26]. One of the main concerns in patients presenting with AF and ACS/MI is the management of dual or triple antithrombotic therapy (OAC plus single or dual antiplatelet therapy) with respect to balancing atherothrombotic, thromboembolic and bleeding risk.

In the antithrombotic decision-making process, a primary distinction has to be drawn between patients presenting with ACS and those undergoing elective percutaneous coronary intervention (PCI) with stent. For patients presenting with ACS and undergoing urgent PCI with stent, almost all the guidelines recommend treatment with triple antithrombotic, with the duration varying from 1-6 months, with shortening of triple therapy based on bleeding risk[13–18]. For example, the recent ACCP guidelines specifically recommend using triple therapy for 6 months in patients with low bleeding risk, shortening duration to1 to 3 months in patients with high bleeding risk, while recommending avoiding it completely in those patients with very high bleeding risk[17]. Following the period of triple therapy, duration of dual antithrombotic therapy should not be continued longer than 12 months after the PCI. In addition, all guidelines indicate a preference for clopidogrel over aspirin as the choice of antiplatelet drug. Recommendations regarding patients with ACS and undergoing urgent PCI (irrespective of stent placement) are generally on the basis of low or moderate quality of evidence[13–18].

Among patients undergoing elective PCI with stent placement, most of the guidelines (ESC, APHRS, NHFA/CSANZ, KHRS) recommend a short duration of triple antithrombotic therapy very short, up to a maximum of 1 month[14–16,19]. According to ACCP guidelines in patients with low bleeding risk, the duration of triple therapy is recommended for 1 month, followed by 12 months of clopidogrel plus OAC; conversely in patients with high risk of bleeding, while the duration of triple therapy is kept to 1 month, the guidelines recommend shortening the dual antithrombotic therapy up to 6 months after the procedure. Finally, in those patients with very high

bleeding risk use of triple therapy is not recommended, and the duration of dual antithrombotic therapy should be kept up to 6 months[17].

The Canadian guidelines recommend a bit different approach. In the 2016 update they did not recommend at all use of triple therapy for elective PCI, suggesting only dual antithrombotic therapy with clopidogrel. In the 2018 version, they changed the recommendations by introducing the use of triple antithrombotic therapy in elective PCI in consideration of the high risk of thrombotic coronary events associated with some clinical variables (i.e. diabetes mellitus, smoking, chronic kidney disease, previous coronary events, etc.) and of type of stent[13,18]. Those patients with high risk features are recommended to be treated for up to 6 months with triple antithrombotic therapy, followed by dual therapy for up to 12 months post stent. However, in patients without high risk features, triple therapy is not recommended[18]. It is important to underline that all the recommendations regarding the use of triple therapy in AF patients receiving elective PCI are weak and based on moderate to low quality of evidence.

Regarding OAC prescription, the CCS, APHRS, KHRS guidelines recommend NOACs over VKAs in ACS patients, although there is less robust evidence[13,15,18,19]. While the NHFA/CSANZ guidelines do not provide any particular recommendation in this regard[16]. The ESC guidelines recommend the use of the lowest approved dosage of NOACs when co-administered with antiplatelet drugs[14], while the ACCP guidelines recommend NOACs as equal to VKAs, but with a weaker recommendation based on a lower quality of evidence[17].

Management of Oral Anticoagulant in Cardioversion and Ablation Procedures

With regard to ablation procedures, all guidelines agree on three main pillars: i) uninterrupted OAC is recommended for patients undergoing ablation procedure; ii) after procedure, OAC therapy is recommended as compulsory for at least 8 weeks in all the patients; iii) long-term OAC prescription beyond the first 8 weeks, should be based on risk profile and proposed only to patients with high risk of stroke[14,15,17–19].

Regarding the type of OAC to be prescribed for pre- and peri-procedural uninterrupted treatment, the ESC, APHRS and CCS 2018 guidelines all recommend NOACs and VKAs as equal alternatives[14,15,18]. As a notable exception, the recent ACCP guidelines only recommend dabigatran or rivaroxaban among the NOACs[17].

With respect to OAC in patients undergoing a cardioversion procedure, all the guidelines agreed on some basic principles: i) in patients with at least 48 hours of proved AF, anticoagulation should be provided for at least 3 weeks to exclude the presence of any left atrial thrombus; ii) as an alternative to OAC, use of a trans-esophageal echocardiogram to exclude the presence of any left atrial thrombus; iii) OAC should be continued for at least 4 weeks after procedure, irrespective of the success of cardioversion procedure[13–19]. Most of the guidelines agree that long-term OAC, irrespective of the success of cardioversion procedure, should be considered on the basis of stroke risk factors[14–19]. Several guidelines also explicitly recommended to provide 3 to 4 weeks OAC treatment if a thrombus is identified on the trans-esophageal echocardiogram[14,15,17,19]. ACCP 2018 and CCS 2018 guidelines provided recommendations regarding specific situations. ACCP guidelines provide an indication about not commencing OAC for patients with <48 hours AF and

hemodynamic instability, rather initiate parenteral anticoagulation as soon as it is possible[17]. In the CCS 2018 guidelines, is indicated that in patients with very short (<12 hours) or short (12-48 hours) AF duration, OAC can be avoided if there is no substantial risk of stroke[18].

Management of OAC in Specific Populations

One of the most debated issues in the management of OAC therapy is the prescription in elderly (very elderly) and frail patients (Table S2). Among the guidelines examined, the CCS (having discussed the issue in the previous 2010 and 2012 versions, but they do not make any recommendations in 2016 and 2018), and APHRS guidelines did not consider this issue[13,15,18].

The ESC guidelines state that the available evidence supports the use of OAC in elderly and frail subjects, due to the high benefit-risk ratio[14]. The NHFA/CSANZ guidelines highlight the beneficial effect of OAC in elderly patients observed in observational registries, with a preference for the use of NOACs, due to the high prevalence of polypharmacy, although caution is recommended with dose-adjustment related to renal function[16]. The ACCP guidelines recommend a specific individual risk assessment prior to OAC prescription while reaffirming that the benefit of OAC prescription generally outweigh the risk of harm from serious bleeding, whilst highlighting a contraindication to OAC prescription is posed for patients with dementia and no caregiver (to administer OAC)[17]. Similar recommendations are included in the KHRS guidelines[19]. Guidelines including specific recommendations about elderly patients did not rate these recommendations.

Another important population is are patients with chronic kidney disease. Impaired renal function is an independent risk factor for stroke, major bleeding and major adverse outcomes in patients with AF[27], thus these patients need careful management in order to maximize stroke prevention and reduce bleeding risk, and the guidelines differ in their recommendations for managing such patients (Table S2) and the lower limit for which OAC use is no longer recommended. Both Canadian guidelines suggest that OAC should not be routinely prescribed for patients with glomerular filtration rate (GFR) <15 mL/min, but that use of OAC may be appropriate in some patients in whom there is a stronger preference in avoiding stroke despite the uncertain benefit and the associated bleeding risk[13,18]. Lack of data, with limited evidence about efficacy and safety of OAC in patients with GFR <30 mL/min and <15 mL/min are claimed by APHRS[15], NHFA/CSANZ[16] and ESC guidelines[14]. Although the APHRS, ACCP and KHRS guidelines recognise the limited evidence, they suggest that use of VKAs with well-managed quality of anticoagulation therapy could be considered[15,17,19].

In patients with moderate to severe CKD (GFR 15-30 mL/min), treatment strategies differ across guidelines. Both Canadian guidelines recommend OAC prescription on the basis of stroke risk, with warfarin the preferred agent[13,18], while the APHRS, ACCP and KHRS guidelines suggest the use of OAC with caution, with the recommendation to reduce NOACs dosages.[15,17,19] The ESC guidelines also recommend reducing the NOAC dosage, although the reduction is suggested for patients with GRF 25-50 mL/min. The adjustment of NOACs dosage is also suggested by the other guidelines for patients with GFR >30 and up to 50 or 60 mL/min, according to guidelines[13,15,17–19]. It is relevant to note that the majority of the

recommendations are weak and based on a low quality of evidence, underlining the need for more solid evidence.

One emergent issue is that related to the treatment of patients with cardiac implantable electronic devices, without clinical AF, that are found to have atrial high rate episodes (AHREs). While some guidelines did not consider this issue[15,19], others suggest that OAC treatment should be considered in those with prolonged AHREs (>24 hours) and a high risk of stroke (CHA_2DS_2-VASc ≥2),[13,16–18] while further data are needed to support the use of OAC in patients with AHREs of shorter duration. However, the ESC guidelines do not advocate OAC treatment for patients with AHREs[14].

Use of an Integrated Management in Patients with Atrial Fibrillation

Given the increased risk for adverse outcomes other than stroke, such as myocardial infarction, cardiovascular death and all-cause death,[9,10,24,25] in AF patients, there is a need for a more integrated and holistic management approach for AF patients, in order to reduce overall cardiovascular risk[11,12]. Most guidelines advocate the need for an integrated approach (Table S3), for example, in the 2016 ESC guidelines, in order to improve adherence to treatment, quality of life and long-term outcomes[14,16–19]. However, the operationalisation and implementation of integrated care needs to be simple and practical. To address the latter, both the ACCP and KHRS guidelines have suggested that use of the 'Atrial Fibrillation Better Care' (ABC)[28] approach as a practical tool to streamline the integrated management of AF patients[17,19].

SUMMARY AND DISCUSSION

In this narrative review, we have discussed the main recommendations regarding OAC management for AF patients from contemporary international guidelines. Most guidelines were compiled with a systematic and well-established approach and rated according to a rigorous evaluation system. There was general agreement in the definition of valvular and non-valvular AF, although some heterogeneity was evident in the temporal classification of AF. Despite not being considered in the OAC decision-making process, the type of AF can influence the risk of major adverse outcomes[29]. Further, the classification of clinical AF influences rate/rhythm management and lack of concordance between the guidelines can be misleading in the evaluation of patients and differing management strategies between physicians.

Evaluation of thromboembolic risk at baseline is very similar across all the guidelines with most adopting the CHA_2DS_2-VASc score, with the notable exception of Canadian guidelines. The almost universal adoption of CHA_2DS_2-VASc score reflects the strength of the current data supporting its' use a clinical risk score that provides a balance between evidence, practicality and precision[30]. A recent comparative effectiveness review about the ability of the scores to predict thromboembolic and bleeding events reported that $CHADS_2$, CHA_2DS_2-VASc and the recent ABC-Stroke[31] scores were best and had a similar predictive capacity for stroke occurrence[32]. Nonetheless, CHA_2DS_2-VASc differs from other scores for its capacity to effectively identify those patients with very low risk and does not require expensive and time-consuming laboratory tests to be undertaken compared to the ABC-Stroke score[30]. Furthermore, recently a systematic review and meta-regression demonstrated that CHA_2DS_2-VASc score represents the score with the highest

probability to perform best in predicting the occurrence of all-cause death in AF patients[33].

The role of the female sex as an independent risk factor, in relation to stroke risk is addressed by all the seven guidelines examined (Table 2)[13–19]. The increased stroke risk in female AF patients has been long discussed[34,35]. A comprehensive meta-analysis including almost 1 million AF patients demonstrated that female patients with AF were at increased risk of stroke, with a 24% of relative risk increase[36]. However, a significant relationship was found between increasing age and a progressively higher risk of stroke in female AF patients[36]. Compelling data from the Danish registries demonstrated that while there were no profound differences between 'low risk' male and female AF patients with no additional stroke risk factors, a sex difference in stroke risk increased with the increasing number of risk factors, suggesting that female sex was "risk modifier" rather than a risk factor per se[37]. Ignoring the female sex criterion would *underestimate* stroke risk in female patients with ≥1 additional stroke risk factor(s), an important consideration when discussing risks with AF patients.

The second pivotal step on which all the guidelines agree is the evaluation of baseline bleeding risk. While five out of 7 of the guidelines examined adopted HAS-BLED as the clinical risk score to evaluate bleeding risk[13,15,17–19], the ESC and NHFA/CSANZ guidelines recognize the utility of the clinical scores to evaluate bleeding risk, but do not recommend the use of any particular score[14,16]. Conversely, these guidelines adopt an approach based on the identification of modifiable and potentially modifiable bleeding risk factors,[14,16] despite evidence demonstrating the

superiority of HAS-BLED to ORBIT, ATRIA Bleeding, HEMORR$_2$HAGES scores[38,39] and to the most recent ABC-Bleeding and GARFIELD-AF Bleeding scores.[40,41] Furthermore, when compared to an approach based exclusively on modifiable bleeding risk factors as promoted by the ESC guidelines, using the HAS-BLED score was a superior strategy for bleeding risk assessment [42,43].

Regarding the prescription of OAC, the Canadian guidelines still recommend prescribing antiplatelet drugs in patients aged <65 years with isolated CAD and no other stroke risk factors[13,18], but all other guidelines support the prescription of OAC in patients with at least one stroke risk factor not related to gender. All the recommendations regarding OAC prescription are strong recommendations and hence supported by solid evidence. Similarly, as largely supported by Phase III randomized clinical trials[2] and observational studies[44–46], all the guidelines recommend the use of NOACs in preference to VKAs. Notwithstanding that globally VKAs are still widely used as OAC, the use of the SAMe-TT$_2$R$_2$ score is mentioned in some guidelines related to where VKAs are used to help assess the likelihood of patients to achieve an optimal anticoagulation control when prescribed with VKAs, that could guide more intense INR monitoring or the alternative prescription of VKAs and NOACs[47].

On the basis of the guideline recommendations and evidence presented, and given that the default should be to offer stroke prevention unless the patient is ‘low risk’, the so-called ‘Birmingham 3-Step’ management strategy has been advocated [Figure 2][1]. In the first step, AF patients who are low risk are identified through CHA$_2$DS$_2$-VASc score, and no antithrombotic therapy is recommended. In the second step,

OAC therapy is considered in all AF patients with at least 1 additional non-sex stroke risk factor(s) and risk of bleeding is assessed, to identify those patients at high risk of bleeding (HAS-BLED ≥3), to address modifiable bleeding risk factors and plan more frequent follow-up checks. In the third step, treatment with OAC should be started with NOACs as the preferred option – and if a VKA is considered, the SAMe-TT_2R_2 score can help to identify those patients that would more likely obtain a low TTR (SAMe-TT_2R_2 >2) who can be identified for more regular INR monitoring, education/counselling or to reconsider being prescribed a NOAC.

Regarding the concomitant use of OAC and antiplatelet drugs, the guidelines examined agree on similar basis. It is recognized that the use of triple antithrombotic therapy in AF with ACS should be based on the balance between atherothrombotic/thromboembolic risk and bleeding risk and that such strategy should be kept as short as possible.

Use of triple antithrombotic therapy has been traditionally associated to an increased risk of bleeding, with several studies reporting an increased rate of major bleeding events with no relative benefit in terms of thromboembolic and atherosclerotic events)[48,49]. For example, the WOEST trial reported that a strategy of clopidogrel plus OAC compared to triple antithrombotic therapy was associated with a lower risk of major bleeding with no difference in terms of efficacy[48]. Nevertheless, if good quality anticoagulation control is attained, the risk of major bleeding in such patients undergoing PCI and stent seems to be significantly reduced[49]. The 2018 joint European consensus document underlined the need to shorten triple antithrombotic therapy in AF patients as much as possible, related to clinical presentation, bleeding

risk, etc[50]. In this situation, a strategy based on NOACs was associated with a reduced risk of major bleeding events[51,52]. However, a network meta-analysis concluded that the best treatment strategy for these high-risk patients still appears to be the use of a VKA and single antiplatelet drugs when considering both efficacy and safety, even though the use of low-dose rivaroxaban appears as a valid alternative[53]. Nevertheless, this network meta-analysis did not include data from the RE-DUAL PCI trial[52]. Future results from other ongoing trials (AUGUSTUS ClinicalTrials.Gov: NCT02415400; ENTRUST-AF-PCI ClinicalTrials.Gov: NCT02866175) will provide further evidence.

In the clinical scenarios of catheter ablation and cardioversion procedures, the guidelines reviewed shared similar approaches regarding the use of OAC and NOACs. Several studies have examined the use of uninterrupted NOACs in the catheter ablation setting and all data support better safety profile compared to VKAs, with no differences in terms of efficacy[54,55]. In the cardioversion setting NOACs were similar to VKAs in terms of both efficacy and safety[56].

With regard to specific populations (patients with chronic kidney disease, the elderly and frail, patients with AHREs), the guidelines highlight the absence of specific controlled studies exploring the efficacy and safety of OAC and NOACs in these populations. Even though observational data are available and subgroups analysis provided some evidence to draft some recommendations, this evidence was not considered solid enough to provide strong recommendations. Future studies are still needed in patients with chronic kidney disease and those elderly and frail to better substantiate current clinical practice. Regarding patients with AHREs, some studies

are currently in progress and will elucidate the risk-benefit ratio of treating these patients with OAC[57,58].

In some of the contemporary guidelines, the need for integrated management for AF patients is highlighted. On the basis of the evidence that AF patients are burdened with an increased risk of major adverse outcomes beyond their mere thromboembolic risks[9,10,24,25], an approach that would account for the multiple issues related to the clinical management of these patients is needed[11,12]. The 2016 ESC guidelines refer to the 'domains of AF management' and the need for a multidisciplinary approach to AF management (with so-called 'Heart Team') but the operationalisation of such an approach requires simple and practical approaches for the AF patient management pathway.

Indeed, the use of an integrated management approach to AF is associated with a reduced risk of all-cause death, cardiovascular death and rehospitalization[59,60 61]. Compliance with the ABC pathway is also associated with reduced healthcare costs[62]. As recently highlighted by some guidelines[17,19], the ABC pathway has been proposed to streamline an integrated and holistic management approach for patients with AF [Figure 3][28].

Significant differences are evicent between the various guidelines examined for some key issues. For example, the CCS guidelines in not indicating the use of OAC in patients <65 years with isolated CAD[13,18] represent one example. This notable exception have been firstly reported in the CCS guidelines in the 2012 update[63] and it stands on the assumption that CAD implies a low risk of stroke in AF patients

(<1.5% per year)[63]. Several data exist show that in AF patients, the presence of vascular disease and CAD are associated to a significant independent increase in stroke risk[64–66].

Even more differences are related to those issues for which a lower quality of evidence and strength of recommendations is available. These reflect the lack of high-quality data obtained from randomized controlled trials and underline the need for future well-designed and adequately powered studies.

The use of an approach based on expert consensus review of the published evidence for the APHRS and KHRS guidelines[15,19] could impact on the daily clinical decision-making process, but when a high quality of evidence is available these guidelines are still able to provide solid recommendations. For all the other aspects for which there is a significant degree of uncertainty, there may be a less objective evaluation of the limited scientific evidence available. In any case, many guidelines that use systematic reviews still include many recommendations with Level of Evidence C, which represents expert consensus anyway.

CONCLUSION

In this narrative review of contemporary guidelines, there is general agreement on the baseline evaluation of thromboembolic and bleeding risk, as well as a preference for the use of NOACs. More data are still needed to better substantiate recommendations for specific AF subpopulations. The need for an integrated approach and holistic management is highlighted in the more recently published guidelines.

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1

FIGURE LEGENDS

Figure 1: Proportion of Papers Related to Atrial Fibrillation in PubMed from Inception to 2017

Legend: AF= Atrial Fibrillation

Figure 2: The 'Birmingham 3-Step' Management Strategy for Anticoagulation in Patients with Atrial Fibrillation

Legend: NOAC= Non-vitamin K Antagonist Oral Anticoagulant; OAC= Oral Anticoagulant; TTR= Time in Therapeutic Range; VKA= Vitamin K Antagonist.

Figure 3: Atrial Fibrillation Better Care (ABC) Pathway for Integrated Care in Atrial Fibrillation Patients

Table 1: Summary of General Characteristics and Definitions of Contemporary Atrial Fibrillation Guidelines

	CCS	ESC	APHRS
Year	2016	2016	2017
Primary Source	CJC 2016; 32 (10)[13]	EHJ 2016; 37 (38)[14]	J Arrhythmia 2017; 33 (4)[15]
Guidelines Methodology	Systematic search according to PICO; GRADE rating of evidence	Systematic search according to PICOT; Experts plenary discussion	Expert Consensus Review
Strength of Recommendations	Strong, Conditional, Weak	Classes I-IIa-IIb-III	Not explicitly assessed
Quality of Evidence	High, Moderate, Low, Very Low	Level A-B-C	Not explicitly assessed
Conflict of Interest Process	Not Reported	Detailed disclosure of all real or potential sources of COI publicly available	Reported in acknowledgment
Classification of AF	New onset, paroxysmal, persistent or permanent	First diagnosed, paroxysmal, persistent, long-standing persistent, permanent	Not explicit
Evaluation of Valvular Origin	Rheumatic mitral stenosis, mitral valve repair, mechanical or bio-prosthetic heart valve	Rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves	Not explicitly assessed

Table 1 (continued): Summary of General Characteristics and Definitions of Contemporary Atrial Fibrillation Guidelines

	NHFA/CSANZ	ACCP	CCS	KHRS
Year	2018	2018	2018	2018
Primary Source	HLC 2018; 27 (10)[16]	Chest 2018;154 (5)[17]	CJC 2018; 34 (11)[18]	KCJ 2018; 48 (12)[19]
Guidelines Methodology	Systematic search according to Clinical Questions; GRADE rating of evidence	Systematic search according to PICO-guided Clinical Questions; GRADE rating of evidence	Systematic search according to PICO; GRADE rating of evidence	Expert Consensus Review
Strength of Recommendations	Strong, Weak	Strong, Weak	Strong, Conditional, Weak	Classes I-IIa-IIb-III
Quality of Evidence	High, Moderate, Low	High, Moderate, Low, Very Low	High, Moderate, Low, Very Low	Level A-B-C
Conflict of Interest Process	Direct or indirect relationship to any third party, both financial and non-financial	Central COIs review. If manageable potential COI, voting on relevant issues was prohibited	Not Reported	Reported in acknowledgment
Classification of AF	Paroxysmal, persistent, long-standing persistent, permanent	Paroxysmal, persistent, long-standing persistent, permanent	New onset, paroxysmal, persistent or permanent	Not explicit
Evaluation of Valvular Origin	Moderate to severe mitral stenosis or mechanical heart valve	Moderate to severe mitral stenosis or mechanical heart valve	Rheumatic mitral stenosis, moderate-severe nonrheumatic mitral stenosis, or a mechanical heart valve	Not explicitly assessed

Legend: APHRS= Asia Pacific Heart Rhythm Society; CCS= Canadian Cardiovascular Society; CJC= Canadian Journal of Cardiology; COI= Conflict of Interest; CSANZ= Cardiac Society of Australia and New Zealand; EHJ= European Heart Journal; ESC= European Society of Cardiology; GRADE= Grading of Recommendations, Assessment, Development and Evaluation; HLC= Heart, Lung and Circulation; KCJ= Korean Circulation Journal; NHFA= National Heart Foundation of Australia; PICO(T)= Population, Intervention, Comparison, Outcome, (Time).

1 **Table 2:** Baseline Thromboembolic Risk Evaluation and Oral Anticoagulation Prescription Algorithm

	CCS	ESC	APHRS
Year	2016	2016	2017
Thromboembolic Risk Assessment	CHADS-65 ('CCS Algorithm')	CHA_2DS_2-VASc	CHA_2DS_2-VASc
Rating of Evidence	Strong Recommendation, High-Quality Evidence	Class I, Level A	Not rated
OAC Prescription Algorithm	i) OAC should be considered for all patients ≥65 years old or with ≥1 $CHADS_2$ risk factors. ii) <65 years old and with arterial disease ASA should be considered	i) OAC is indicated in all patients with a CHA_2DS_2-VASc ≥2, excluding sex category ii) OAC should be considered in all patients with just 1 CHA_2DS_2-VASc risk factors, excluding sex category	OAC is indicated in all patients with a CHA_2DS_2-VASc ≥1, excluding sex category
Rating of Evidence	i) Strong Recommendation, Moderate-Quality Evidence ii) Conditional Recommendation, Moderate-Quality Evidence	i) Class I, Level A ii) Class IIa, Level B	Not rated
Use of NOACs	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of Evidence	Strong Recommendation, High-Quality Evidence	Class I, Level A	Not rated

2

Table 2 (continued): Baseline Thromboembolic Risk Evaluation and Oral Anticoagulation Prescription Algorithm

	NHFA/CSANZ	ACCP	CCS	KHRS
Year	2018	2018	2018	2018
Thromboembolic Risk Assessment	CHA_2DS_2-VA	CHA_2DS_2-VASc	CHADS-65 ('CCS Algorithm')	CHA_2DS_2-VASc
Rating of Evidence	Strong Recommendation, Moderate-Quality Evidence	Strong Recommendation, Moderate-Quality Evidence	Strong Recommendation, High-Quality Evidence (2014)	Class I, Level A
OAC Prescription Algorithm	i) OAC is indicated in all patients with CHA_2DS_2-VA ≥2 ii) OAC should be considered in all patients with CHA_2DS_2-VA 1	OAC is indicated in all patients with a CHA_2DS_2-VASc ≥1, excluding sex category	i) OAC should be considered for all patients ≥65 years old or with ≥1 $CHADS_2$ risk factors. ii) <65 years old and with arterial disease ASA should be considered	i) OAC is indicated in all patients with a CHA_2DS_2-VASc ≥2, excluding sex category ii) OAC should be considered in all patients with just 1 CHA_2DS_2-VASc risk factors, excluding sex category
Rating of Evidence	i) Strong Recommendation, High-Quality Evidence ii) Strong Recommendation, Moderate-Quality Evidence	Strong Recommendation, Moderate-Quality Evidence	i) Strong Recommendation, Moderate-Quality Evidence ii) Conditional Recommendation, Moderate-Quality Evidence (2014)	i) Class I, Level A ii) Class IIa, Level B
Use of NOACs	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of Evidence	Strong Recommendation, Moderate-Quality Evidence	Strong Recommendation, Moderate-Quality Evidence	Strong Recommendation, High-Quality Evidence (2014)	Class I, Level A

Legend: ASA= Acetylsalicylic acid; CHADS= Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke/Transient Ischemic Attack; CHA_2DS_2-VASc= Congestive Heart Failure, Hypertension, Age≥75 years, Diabetes Mellitus, Stroke/Transient

Ischemic Attack, Vascular Disease, Age 65-74 years, Sex category; NOAC= Non-vitamin K antagonist oral anticoagulant; OAC= Oral anticoagulant; VKA= Vitamin K Antagonist; for other acronyms please see Table 1 legend.

Table 3: Baseline Bleeding Risk Evaluation and Associated Recommendations

	CCS	ESC	APHRS
Year	2016	2016	2017
Bleeding Risk Assessment	HAS-BLED	Use of clinical risk scores to evaluate modifiable and potentially modifiable risk factors for major bleeding	HAS-BLED
Rating of Evidence	Strong Recommendation, High-Quality Evidence (2010)	Class IIa, Level B	Not rated
Associated Recommendation	Adopt specific measures to mitigate bleeding risk factors	Not withhold OAC. Identify and correct modifiable bleeding risk factors	For patients with HAS-BLED ≥3 not withhold OAC and provide regular review and follow-up of the modifiable bleeding risk factors.

Table 3 (continued): Baseline Bleeding Risk Evaluation and Associated Recommendations

	NHFA/CSANZ	ACCP	CCS	KHRS
Year	2018	2018	2018	2018
Bleeding Risk Assessment	Identification of reversible bleeding risk factors	HAS-BLED	HAS-BLED	HAS-BLED
Rating of Evidence	Strong Recommendation, Low-Quality of Evidence	Strong Recommendation, Moderate-Quality of Evidence	Strong Recommendation, High-Quality Evidence (2010)	Class I, Level A
Associated Recommendation	Minimisation of bleeding risk through treating of reversible risk factors	HAS-BLED ≥3 should not be a reason to withhold OAC. Those patients at higher bleeding risk is warranted for more frequent and regular reviews and follow-up	Adopt specific measures to mitigate bleeding risk factors	A high bleeding risk is not a reason to withhold OAC treatment. Modifiable bleeding risk factors should be addressed to reduce bleeding risk

Legend: HAS-BLED= Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile anticoagulation quality, Elderly, Drugs or alcohol; for other acronyms please see previous tables legends.

1 **Table 4:** Combination of OAC with Antiplatelet Drugs in patients with Concomitant Cardiac Disease

	CCS	ESC	APHRS
Year	2016	2016	2017
Patients with ACS	i) In patients <65 years old and no $CHADS_2$ risk factors 12 months treatment with aspirin and P2Y12 inhibitor (chosen according to risk and implementation of PCI) with indefinite treatment with aspirin if PCI has been performed ii) In patients ≥65 years old and $CHADS_2$ ≥1 and no PCI is undertaken clopidogrel 75 mg and OAC for 12 months followed by only OAC iii) In patients ≥65 years old and $CHADS_2$ ≥1 and PCI is undertaken ASA 81 mg + clopidogrel 75 mg + OAC for 3/6 months (according to risk) followed by clopidogrel 75 mg + OAC up to 12 months then OAC	i) In patients not undergoing PCI dual therapy with OAC and aspirin or clopidogrel should be considered up to 12 months ii) In patients undergoing PCI triple therapy with OAC, aspirin and clopidogrel should be considered from 1 to 6 months on the basis of bleeding risk, followed by dual therapy with aspirin or clopidogrel iii) Duration of combination therapy, especially triple therapy, should be kept to the minimum, balancing risk of bleeding and recurrent events	In patients with ACS triple therapy can be continued from 1 to 6 months according to bleeding risk (high or low) with dual therapy up to 12 months after the event
Rating of Evidence	i) Strong Recommendation, High-Quality Evidence ii) Conditional Recommendation, Low-Quality Evidence iii) Conditional Recommendation, Low-Quality Evidence	i) Class IIa, Level C ii) Class IIa, Level C iii) Class IIa, Level B	Not rated
Elective PCI	i) In patients <65 years and no $CHADS_2$	i) In patients undergoing elective PCI, use	In patients with elective PCI triple therapy

	risk factors indefinite treatment with aspirin + 12 months of treatment with clopidogrel is recommended ii) In patients ≥65 and $CHADS_2$ risk factors OAC + clopidogrel with no aspirin are indicated for 12 months followed by indefinite OAC	of triple therapy with OAC, aspirin and clopidogrel should be limited to 1 month ii) Dual therapy with OAC and aspirin or clopidogrel, could be continued up to 6 or 12 months according to bleeding risk	should be continued for 1 month, with dual therapy continued up to 6 or 12 months, according to bleeding risk (high or low)
Rating of Evidence	i) Strong Recommendation, High-Quality Evidence ii) Strong Recommendation, High-Quality Evidence	i) Class IIa, Level B ii) Class IIa, Level C	Not rated
Use of NOACs	When OAC indicated a NOAC is preferred over warfarin	When NOAC is used the lowest recommended dose should be administered together with antiplatelet therapy	A NOAC is preferred over warfarin
Rating of Evidence	Not rated	Not rated	Not rated

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1 **Table 4 (continued):** Combination of OAC with Antiplatelet Drugs in patients with Concomitant Cardiac Disease

	NHFA/CSANZ	ACCP	CCS	KHRS
Year	2018	2018	2018	2018
Patients with ACS	i) In patients with ACS or PCI duration of triple therapy should be kept as short as possible to minimize risk of bleeding, still ensuring the coverage of the high risk of recurrent event/stent thrombosis ii) After triple therapy, dual therapy with OAC and aspirin 100 mg or clopidogrel 75 mg is recommended	i) In patients with ACS and low bleeding risk, triple therapy is suggested up to 6 months, followed by OAC plus single antiplatelet (preferably clopidogrel) up to 12 months ii) In patients with ACS and high bleeding risk, triple therapy is suggested from 1 to 3 months, followed by OAC plus antiplatelet (preferably clopidogrel) up to 12 months iii) In patients with very high bleeding risk, a strategy with OAC and single antiplatelet (preferably clopidogrel) for 6-9 months is suggested	i) In patients ≤65 years and no $CHADS_2$, use of antiplatelet therapy according to characteristics and extent of disease as directed by other guidelines ii) In patients ≥65 years and $CHADS_2$ ≥1 not undergoing PCI, OAC plus P2Y12 inhibitor (preferably clopidogrel) is indicated for 12 months iii) In patients ≥65 years and $CHADS_2$ ≥1 undergoing PCI, OAC, aspirin and clopidogrel are indicated up to 6 months, followed by OAC plus clopidogrel up to 12 months	No recommendation
Rating of Evidence	i) Strong Recommendation, Moderate-Quality of Evidence ii) Strong Recommendation, Low-Quality of Evidence	i) Weak Recommendation, Low-Quality of Evidence ii) Weak Recommendation, Low-Quality of Evidence iii) Weak Recommendation,	i) Not rated ii) Weak Recommendation, Low-Quality of Evidence iii) Weak Recommendation, Moderate-Quality of Evidence	-

		Low-Quality of Evidence		
Elective PCI	i) In patients with ACS or PCI duration of triple therapy should be kept as short as possible to minimize risk of bleeding, still ensuring the coverage of the high risk of recurrent event/stent thrombosis ii) After triple therapy, dual therapy with OAC and aspirin 100 mg or clopidogrel 75 mg is recommended	i) In patients receiving PCI and low bleeding risk, triple therapy is suggested for 1 month, followed by OAC plus single antiplatelet (preferably clopidogrel) up to 12 months ii) In patients receiving PCI and high bleeding risk, triple therapy is suggested for 1 month, followed by OAC plus antiplatelet (preferably clopidogrel) up to 6 months iii) In patients with very high bleeding risk, a strategy with OAC and single antiplatelet (preferably clopidogrel) for 6 months is suggested	i) In patients ≥65 years and $CHADS_2$ ≥1 receiving PCI without high-risk features, OAC plus clopidogrel is suggested for at least 1 month (BMS) or at least 3 months ii) In patients ≥65 years and $CHADS_2$ ≥1 receiving PCI with high-risk features, OAC, aspirin and clopidogrel are indicated up to 6 months, followed by OAC plus clopidogrel up to 12 months	Triple therapy is recommended to be as short as possible, in relation to bleeding risk, unless the risk of stent thrombosis/recurrence would not be too high. After triple therapy, dual therapy with OAC and P2Y12 inhibitor (preferably clopidogrel) should be continued up to 12 months after PCI.
Rating of Evidence	i) Strong Recommendation, Moderate-Quality of Evidence ii) Strong Recommendation, Low-Quality of Evidence	i) Weak Recommendation, Low-Quality of Evidence ii) Weak Recommendation, Low-Quality of Evidence iii) Weak Recommendation, Low-Quality of Evidence	i) Weak Recommendation, Moderate-Quality of Evidence ii) Weak Recommendation, Moderate-Quality of Evidence	Not rated
Use of NOACs	No specific recommendation done.	NOACs are indicated equally to VKAs	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of	-	Weak Recommendation,	Weak Recommendation,	Not rated

Evidence	Low-Quality of Evidence	Moderate-Quality of Evidence

Legend: ACS= Acute Coronary Syndrome; PCI= Percutaneous Coronary Intervention; for other acronyms please see previous tables legends.

Table 5: Oral Anticoagulation Management in Patients Undergoing Ablation or Cardioversion Procedure

	CCS	ESC	APHRS
Year	2016	2016	2017
Ablation Procedure	OAC should be continued after AF surgical ablation according to CCS algorithm	i) All patients should receive OAC for at least 8 weeks after catheter ablation ii) OAC should be continued indefinitely after successful catheter ablation in patients at high risk of stroke iii) Continuation of OAC with VKAs or NOACs during procedure is recommended	i) NOACs can be safe and effective alternatives to VKAs for periprocedural anticoagulation ii) OAC should be continued for at least 3 weeks before procedure in patients with at least 48 H of AF iii) OAC should be continued for at least 2 months after ablation, and longer in those patients with high risk of stroke
Rating of Evidence	Strong Recommendation, Moderate-Quality of Evidence	i) Class IIa, Level B ii) Class IIb, Level C iii) Class IIb, Level B (VKAs) or Level C (NOACs)	Not rated
Cardioversion Procedure	OAC should be prescribed for 3 weeks before cardioversion and at least 4 weeks after. If AF recurs OAC should be prescribed on the basis of the CCS algorithm. If SR is achieved, decision on continuing OAC after 4 weeks of treatment should be based on risk of stroke and upon expert consultation	i) Effective anticoagulation is recommended for at least 3 weeks before cardioversion ii) Anticoagulation with heparin or NOAC should be initiated before every cardioversion procedure iii) In patients without stroke risk factors anticoagulation is recommended for 4 weeks. In those at risk of stroke anticoagulation should be continued long-term after procedure iv) Perform TEE is recommended as an alternative to OAC v) If with TEE a thrombus is identified 3	i) Anticoagulation is needed 3 weeks before and 4 weeks after cardioversion procedure ii) In patients undergoing TEE, if thrombus is identified OAC is needed for at least 4 weeks and repeat TEE to ensure thrombus resolution ii) After cardioversion long-term OAC is needed in patients with high risk of stroke iv) For OAC in patients undergoing cardioversion both VKAs and NOACs can be considered

		weeks OAC is recommended	
Rating of Evidence	Strong Recommendation, Moderate-Quality of Evidence	i) Class I, Level B ii) Class IIa, Level B iii) Class I, Level B iv) Class I, Level B v) Class I, Level C	Not rated

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Table 5 (continued): Oral Anticoagulation Management in Patients Undergoing Ablation or Cardioversion Procedure

	NHFA/CSANZ	ACCP	CCS	KHRS
Year	2018	2018	2018	2018
Ablation Procedure	Uninterrupted OAC is recommended for patients undergoing catheter ablation	i) OAC with VKA, dabigatran or rivaroxaban is recommended for patients undergoing ablation ii) After ablation long-term OAC should be prescribed on the basis of thromboembolic risk profile	Use of uninterrupted OAC, either with NOACs or VKAs is recommended	i) Uninterrupted OAC is recommended for patients undergoing catheter ablation ii) OAC after ablation should be continued for at least 2 months iii) After 2 months, long-term OAC should be decided on patient's stroke risk
Rating of Evidence	Strong Recommendation, Moderate-Quality of Evidence	i) Weak Recommendation, Low-Quality of Evidence ii) Weak Recommendation, Low-Quality of Evidence	Weak Recommendation, Moderate-Quality of Evidence	Not rated
Cardioversion Procedure	i) OAC for 3 weeks is recommended (or TEE to document absence of left atrium thrombus) before cardioversion procedure ii) OAC is recommended for at least 4 weeks after cardioversion procedure	i) In patients with AF for 48H or more OAC with VKAs or NOACs is recommended at least 3 weeks before cardioversion or TEE approach with abbreviated OAC treatment ii) In patients with 48H or less AF or hemodynamic instability, parenteral anticoagulation should be started as soon as possible before procedure and continued for at least 4 weeks	i) Patients planned to receive cardioversion should receive OAC for 3 weeks before procedure ii) 3 weeks OAC treatment can be waived if AF is <12 with no recent stroke or within 12 and 48 hours and there is no substantial stroke risk iii) OAC is recommended to be	i) OAC is recommended for at least 3 weeks before cardioversion ii) After procedure OAC is recommended for at least for 4 weeks in patients without stroke risk factors. In patients at risk of stroke, long-term OAC is recommended iii) Anticoagulation with heparin or NOAC should be initiated as soon as possible before every

		iii) After cardioversion, OAC with VKAs or NOACs should be continued for at least 4 weeks. Continuing OAC beyond 4 weeks should be based on general OAC prescription decision making	continued for at least 4 weeks iv) TEE can be considered as an alternative to OAC v) Both NOACs and heparin/VKAs strategies can be used vi) OAC continuation after 4 weeks should be decided on the basis of CCS algorithm	cardioversion procedure iv) If a TEE identify a thrombus in left atrium, effective anticoagulation is recommended for at least 3 weeks
Rating of Evidence	i) Strong Recommendation, Low-Quality of Evidence	i) Strong Recommendation, Moderate-Quality of Evidence ii) Weak Recommendation, Low-Quality of Evidence iii) Strong Recommendation, Moderate-Quality of Evidence	i) Strong Recommendation, Moderate-Quality of Evidence ii) Weak Recommendation, Low-Quality of Evidence iii) Weak Recommendation, Low-Quality of Evidence iv) Weak Recommendation, Moderate-Quality of Evidence v) Weak Recommendation, Low-Quality of Evidence vi) Strong Recommendation, Moderate-Quality of Evidence	i) Class I, Level B ii) Class I, Level B iii) Class IIa, Level B iv) Class I, Level C

1 **Legend:** SR= Sinus Rhythm; TEE= Trans-Esophageal Echocardiography; for other acronyms please see previous tables legends.

2